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Risk factors for carbapenem-resistant *Klebsiella pneumoniae* infection in a palliative care centre

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Abstract

Introduction: *Klebsiella pneumoniae* (KP) is a gram-negative bacterium in the *Enterobacteriaceae* family. It is common among patients receiving palliative care. This study aimed to examine the risk factors for carbapenem-resistant KP (CRKP) infection in our palliative care unit.

Material and methods: This retrospective observational study was conducted in patients found to have KP infection in the palliative care centre of our hospital. Culture results were identified through the microbiological laboratory database. The patients' demographic and clinical characteristics were obtained from hospital electronic records. The Charlson Comorbidity Index (CCI) was calculated retrospectively for each patient.

Results: The median age of the 88 patients included in the study was 73 years, and 54 (61.4%) were male. The isolated pathogen was CRKP in 55 patients (62.5%). The presence of central venous catheter, tracheostomy, urinary catheter, and intensive care follow-up before admission to the palliative care unit were significantly more common in patients with CRKP-positive cultures. The presence of significant risk factors for carbapenem resistance and univariate logistic regression were used to create a logistic regression model. The results indicated that parenteral nutrition and CCI were independent risk factors that increased the risk of CRKP infection by 3.704 and 1.447 times, respectively.

Conclusions: The prevalence of CRKP is higher in patients receiving parenteral nutritional support. This demonstrates the importance of early transition to enteral nutrition if there is no contraindication. High CCI is a significant risk factor for the development of CRKP infection.

Key words: carbapenem-resistant *Klebsiella pneumoniae*, infection, risk factor, palliative care.

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INTRODUCTION

Palliative care is a medical specialty involving multidisciplinary collaboration to support optimal quality of life by preventing or alleviating pain and suffering in individuals with serious illness [1]. Patients receiving palliative care support have a high rate of infection due to factors such as advanced age, steroid use, drug- or disease-induced immunosuppression, delirium, immobilization, catheterization, tracheostomy, and prolonged hospitalization. Infectious diseases are among the parameters that reduce quality of life in these patients [2].

Klebsiella pneumoniae (KP) is a gram-negative bacterium in the *Enterobacteriaceae* family that is found in the human and animal gastrointestinal tract. It is frequently detected in community-acquired and nosocomial infections. In our country, as of 2020, KP carbapenem resistance has reached almost 50% in intensive care units. It is frequently encountered in our practice in patients receiving palliative care in which patients with similar risks are followed [3]. Effective infection control measures and appropriate antibiotherapy directly affect survival in these infections [4, 5].

Although the discovery of antibiotics is one of the greatest human achievements of the 20th cen-

tury, their effectiveness is limited by the potential development of resistance [6]. Carbapenem-resistant KP (CRKP) has emerged as a significant threat because of its increased incidence worldwide since the turn of the century, the lack of safe and effective therapeutic agents should carbapenems fail, and the high mortality rates associated with these infections [7, 8]. Therefore, CRKP has been recognized by the World Health Organization as one of the critical priority pathogens for which new antimicrobials are needed [9]. Risk factors for CRKP infection include long-term hospitalization, use of antibiotherapy, intensive care follow-up, use of multiple antibiotics, immunosuppression, invasive medical procedures, and history of previous infection. Risk factors for mortality have been shown to include mechanical ventilation, septic shock, and isolation of CRKP [10].

Our palliative care unit was established in 2019 and has a capacity of 21 beds. Since the establishment of our unit, we have observed a high incidence of KP infection. To the best of our knowledge, there has been no previous investigation of KP infections and associated risk factors in palliative care centres in our country. Therefore, this study aimed to examine the risk factors for CRKP infection in our palliative care unit.

MATERIAL AND METHODS

This retrospective observational study was conducted in patients found to have KP infection in the palliative care centre of our hospital between 1 January 2019 and 1 June 2022. Culture results were identified through the microbiological laboratory database. The patients' demographic and clinical characteristics were obtained from hospital electronic records. The Charlson Comorbidity Index (CCI) was calculated retrospectively for each patient [11]. In addition, we recorded the following patient data:

- ward prior to palliative care admission,
- reasons for admission to the palliative care unit,
- laboratory values at admission to palliative care,
- antibiotic use at admission to palliative care,
- presence of vascular catheter, urinary catheter, tracheostomy, and percutaneous endoscopic gastrostomy (PEG),
- history of intensive care follow-up before admission to palliative care,
- feeding method,
- date of KP-positive culture,
- laboratory data at time of KP-positive culture,
- length of hospital stay at time of KP-positive culture,
- positive culture site,
- antibiotic susceptibility of isolates,
- antibiotherapy received (drug and duration),
- presence and type of other microorganisms cultured after treatment,
- day of admission to the palliative care unit,
- discharge date,
- discharge type,
- laboratory data at discharge.

Statistical analysis

All data were imported to and analysed in the SPSS for Windows version 21 (SPSS Inc., Chicago, IL, USA) statistical package program. Categorical data were presented as frequency and percentage, and continuous variables as mean, standard deviation, median, and range. Comparisons of categorical data between groups were made using χ^2 test or Fisher's exact test if the value in any cell was < 5. Continuous data were found to be non-normally distributed and were analysed using non-parametric Kruskal-Wallis and Mann-Whitney *U* tests. Categorical and continuous variables found to be significant in terms of carbapenem resistance were used to create a multivariate logistic regression model (Model: Enter, Entry: 0.05, and Removal: 0.10). *P*-values < 0.05 were considered statistically significant.

Permission to conduct the study was obtained from the Atatürk University Faculty of Medicine Clinical Research Ethics Committee (decision number 04, dated 29/09/2022).

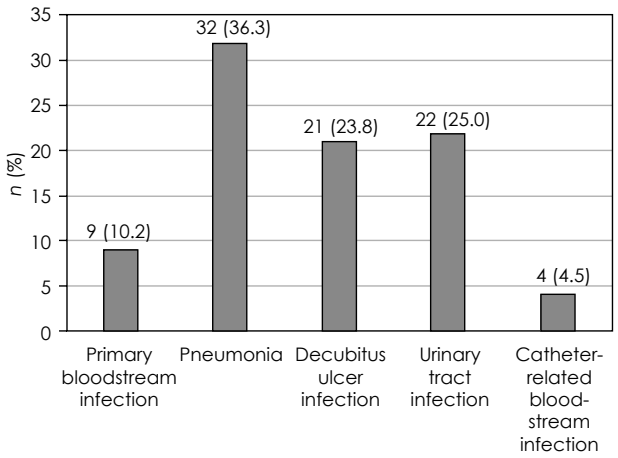

Fig. 1. Foci of infections in which *Klebsiella pneumoniae* was isolated as the causative microorganism

RESULTS

The median age of the 88 patients included in the study was 73 years (range: 21–96), and 54 (61.4%) were male. The distribution of infection foci in which KP was isolated as the causative microorganism during follow-up in the palliative care unit is presented in Figure 1.

The isolated pathogen was CRKP in 55 patients (62.5%) and carbapenem-sensitive KP in 33 patients (37.5%). Comparisons of the reasons for hospitalization according to carbapenem susceptibility are shown in Table 1. CRKP was isolated in all patients admitted for PEG, but this factor could not be analysed statistically because of the lack of patients in the carbapenem-susceptible group.

The distributions of underlying diseases and selected risk factors present before the isolation of KP in the palliative care unit in patients with carbapenem-resistant and -sensitive KP isolates are presented in Table 2. The presence of central venous catheter, tracheostomy, urinary catheter, and intensive care follow-up before admission to the palliative care unit were significantly more common in patients with CRKP-positive cultures. In addition, patients in whom CRKP was isolated had a significantly longer stay in the palliative care unit and higher median CCI compared to those with carbapenem-sensitive isolates.

The frequency of antibiotic use at admission to the palliative care unit and the antibiotic groups used compared according to carbapenem sensitivity results is evaluated in Table 3. Antibiotherapy at palliative care admission was more common among patients with CRKP than in those with carbapenem-sensitive KP. CRKP was detected in all patients who had previously used piperacillin/tazobactam. However, statistical analysis was not possible bcause there were no patients in the carbapenem-sensitive group.

Comparisons of laboratory markers evaluated at the time of KP isolation according to carbapenem sensitivity results are presented in Table 4. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transferase (GGT) levels were significantly higher in patients with CRKP isolates. When the relationship between these biomarkers and other risk factors was evaluated, we observed a significant relationship between patients who underwent PEG and those treated with piperacillin/tazobactam, all of whom were diagnosed with CRKP infection. AST, ALT, and GGT values were found to be significantly higher in patients who underwent PEG ($p = 0.001$, $p = 0.001$, and $p < 0.001$, respectively), while ALT and GGT values were significantly higher in patients who used piperacillin/tazobactam ($p = 0.029$ and $p = 0.001$, respectively).

Univariate and multivariate logistic regression analyses of the variables identified as risk factors for carbapenem resistance are presented in Table 5. Presence of central venous catheter, tracheostomy, history of intensive care, parenteral nutrition, use of antibiotics at admission to palliative care, CCI, and AST and GGT values at time of KP-positive culture were found to be significant risk factors for carbapenem resistance in univariate logistic regression and were used to create the logistic regression model. The results indicated that parenteral nutrition and high CCI value were independent risk factors that increased the risk of CRKP infection by 3.704 and 1.447 times, respectively.

DISCUSSION

Carbapenem resistance in KP has exceeded 25% in one-third of countries, posing a major problem [12, 13]. This problem has become one of the greatest

Table 1. Distribution of reasons for hospitalization according to carbapenem susceptibility result

Parameters	Carbapenem		*p*
Reasons for hospitalization	**Resistant (*n* = 55)**	**Sensitive (*n* = 33)**	
Malnutrition	15 (27.3)	15 (45.5)	0.082
Decubitus wound	18 (32.7)	15 (45.5)	0.233
Pneumonia	13 (23.6)	10 (30.3)	0.491
To make a discharge plan	16 (29.1)	8 (24.2)	0.621
PEG tube insertion	9 (16.4)	–	NA
Delirium	1 (1.8)	1 (3.0)	0.612
Hypernatremia	3 (5.5)	5 (15.2)	0.126
Hyponatremia	1 (1.8)	1 (3.0)	0.612
Symptomatic anaemia	–	1 (3.0)	0.375
Hypercalcemia	1 (1.8)	–	NA
Rehabilitation	17 (30.9)	8 (24.2)	0.502
Oncologic emergencies	–	1 (3.0)	0.375
Pain palliation	3 (5.5)	4 (12.1)	0.235

χ^2 and Fisher's exact test (if any cell is < 5); number and column percentages are given.

Table 2. The distribution of comorbidities and selected risk factors preceding *Klebsiella pneumoniae* isolation in the palliative care unit according to antibiogram susceptibility results

Comorbidity/risk factor	Carbapenem		p
	Resistant (*n* = 55)	Sensitive (*n* = 33)	
HT	33 (60.0)	15 (45.5)	0.185
DM	19 (34.5)	12 (36.4)	0.863
CAD	11 (20.0)	10 (30.3)	0.272
CRF	5 (9.1)	6 (18.2)	0.212
CHF	5 (9.1)	5 (15.2)	0.386
CVD	28 (50.9)	15 (45.5)	0.620
Dementia	18 (32.7)	12 (36.4)	0.728
Parkinson's disease	1 (1.8)	–	NA
COPD	5 (9.1)	4 (12.1)	0.454
Asthma	1 (1.8)	–	NA
Chronic liver disease	1 (1.8)	–	NA
Peripheral vascular disease	2 (3.6)	2 (6.1)	0.482
Malignancy	10 (18.2)	7 (21.2)	0.727
Hypothyroidism	6 (10.9)	1 (3.0)	0.183
Number of comorbidities, median (range)	3 (1–8)	3 (0–7)	0.892
CCI, median (range)	6 (1–13)	4 (1–8)	0.010
Presence of central venous catheter	27 (49.1)	7 (21.2)	0.009
Presence of tracheostomy	24 (43.6)	5 (15.2)	0.005
Presence of urinary catheter	49 (89.1)	29 (87.9)	0.862
Parenteral nutrition	31 (49.1)	7 (21.2)	0.009
Intensive care follow-up	34 (61.8)	12 (36.4)	0.021
Days in hospital before KP-positive culture, median (range)	17 (2–142)	8 (1–45)	0.032

CAD – coronary artery disease, CCI – Charlson Comorbidity Index, CHF – congestive heart failure, COPD – chronic obstructive pulmonary disease CRF – chronic renal failure, CVD – cerebrovascular disease, DM – diabetes mellitus, HT – hypertension
χ^2 and Fisher's exact test (if any cell is < 5); number and column percentage are given unless otherwise specified.

Table 3. Distribution of carbapenem susceptibility results according to antibiotic use at admission to the palliative care unit and antibiotic group

Parameters	Carbapenem		p
Antibiotic use at admission	**Resistant (*n* = 55)**	**Sensitive (*n* = 33)**	
Antibiotic use at palliative care admission	32 (58.2)	10 (30.3)	0.011
Meropenem	10 (18.2)	4 (12.1)	0.332
Ceftriaxone	2 (3.6)	4 (12.1)	0.138
Ciprofloxacin	2 (3.6)	1 (3.0)	0.686
Piperacillin/tazobactam	5 (9.1)	–	NA
Colistin	3 (5.5)	1 (3.0)	0.518
Amikacin	2 (3.6)	–	NA
Tigecycline	3 (5.5)	1 (3.0)	0.518
Linezolid	3 (5.5)	1 (3.0)	0.518
Amoxicillin/clavulanate	1 (1.8)	–	0.625
Ampicillin/sulbactam	7 (12.7)	1 (3.0)	0.123
Moxifloxacin	2(3.6)	–	NA
Vancomycin	4 (7.3)	–	NA
Fosfomycin	1 (1.8)	–	NA

χ^2 and Fisher's exact test (if any cell is <5); number and column percentages are given.

threats to public health because of the few effective treatments available and the limited production of new antibiotics [7]. Identifying the risk factors for CRKP infection can help clinicians predict infection early and take necessary measures to reduce transmission, thereby decreasing infection rates [14]. It is very difficult to follow up high-risk frail patients with CRKP infections in palliative care units and to manage the antibiotics used in treatment considering their adverse effect profiles and the reimbursement policies in our country. This demonstrates the importance of identifying CRKP risk factors in palliative care units, which is the purpose of our study.

In the literature, risk factors for acquiring CRKP infection have been identified in different patient groups [13–16]. In a systemic review evaluating risk factors for CRKP, the presence of central venous catheter, tracheostomy, intensive care, previous antibiotic use, prolonged hospital stay, and parenteral nutrition were found to be risk factors, as in our study conducted in the a palliative care unit [16]. Invasive procedures disrupt the human body's normal barrier to the external environment. Opportunistic pathogens form biofilms on the instruments used for these interventions, which makes them difficult to eradicate. Pathogenic bacteria easily adhere to catheters or the inner walls of tracheostomy tubes and enter deep tissues, increasing the risk of CRKP infection [17, 18]. Selective pressure by previously used antibiotics is regarded as one of the main causes of CRKP infections [16]. Previous studies have shown that the use of various antibiotic groups is a risk factor for CRKP infection [13, 15, 16, 19]. Antibiotic use was also identified as a risk factor in our study. Although the frequency of CRKP was higher for all antibiotic groups, no statistical relationship was found. We believe this to be related to the limited number of patients in each antibiotic group. Our results also showed that elevated ALT, AST, and GGT values were risk factors for CRKP infections. The main causes of this were found to be related to previous use of piperacillin/tazobactam and undergoing PEG.

The Charlson Comorbidity Index is a widely used assessment method that is easy, rapid, and effective in predicting mortality, including from CRKP infections [20–22]. In a study conducted in Korea, the presence of a vascular catheter and a high CCI score were found to be independent risk factors for carbapenem-resistant *Enterobacteriaceae* acquisition [23]. In another study, a CCI of 4 or higher was one of the independent risk factors in a risk model created to identify patients with possible carbapenem-resistant *Enterobacteriaceae* infection [24]. The Charlson Comorbidity Index was also found to be an independent risk factor in our study, with a one-unit increase in CCI increasing the risk of CRKP infection by 1.447 times.

Table 4. Distribution of laboratory markers evaluated at time of *Klebsiella pneumoniae* isolation according to carbapenem susceptibility results

Parameters	Carbapenem		*p*
Laboratory markers	**Resistant (*n* = 55)**	**Sensitive (*n* = 33)**	
WBC count [µl/ml]	8830 (2160–16360)	8740 (3560–23270)	0.257
Neutrophil count	5740 (1280–14380)	6600 (1470–21080)	0.095
Lymphocyte count [mcl]	1660 (100–3830)	1300 (400–3510)	0.099
Platelet count [10^9/l]	281000 (20000–602000)	277000 (21000–514000)	0.361
MPV [fl]	10.2 (8.8–14.4)	10.2 (8.8–13.4)	0.931
BUN [mg/dl]	17.29 (5.14–97.2)	27.1 (6–106.54)	0.080
Creatinine [mg/dl]	0.47 (0.13–3.53)	0.56 (0.09–2.29)	0.193
Sodium [mmol/l]	139 (131–155)	136 (123–151)	0.155
Potassium [mmol/l]	3.76 (2.16–5.38)	3.67 (2.54–5.78)	0.241
Calcium [mg/dl]	8.3 (6.72–9.9)	8.4 (6.8–11.84)	0.87
Glucose [mmol/l]	97 (50–501)	103 (71–376)	0.904
AST [U/l]	25 (4.6–102)	20 (8–56)	0.002
ALP [U/l]	16.9 (3.4–204)	12 (3–66)	0.033
ALP [U/l]	103 (27–1719)	89 (42–233)	0.143
GGT [U/l]	41 (11–317)	21 (10–147)	0.001
CRP [mg/l]	59.41 (1.93–345.95)	77.48 (3.48–235.21)	0.106
Procalcitonin [ng/ml]	0.2 (0.02–26)	0.23 (0.04–42.1)	0.928

ALP – alkaline phosphatase, AST – aspartate aminotransferase, BUN – blood urea nitrogen, CRP – C-reactive protein, GGT – gamma-glutamyl transferase, MPV– mean platelet volume, WBC – white blood cells
Median and range values are given.

Table 5. Univariate and multivariate logistic regression analysis of variables identified as risk factors for carbapenem resistance

Risk factors for carbapenem resistance	Univariate OR (% 95 GA)	p	Multivariate OR (% 95 GA)	p
Presence of central venous catheter	3.582 (1.334–9.619)	0.011	1.640 (0.366–7.362)	0.518
Presence of tracheostomy	4.335 (1.457–12.903)	0.008	2.724 (0.608–12.203)	0.190
Parenteral nutrition	3.582 (1.334–9.619)	0.011	3.704 (1.114–12.317)	0.033
Intensive care follow-up	3.062 (1.249–7.511)	0.014	1.045 (0.220–4.972)	0.956
Days in hospital before KP-positive culture	0.974 (0.945–1.003)	0.082		
Antibiotic use at palliative care admission	3.200 (1.281–7.994)	0.013	2.27 (0.707–7.010)	0.171
CCI	1.435 (1.137–1.812)	0.002	1.447 (1.085–1.930)	0.012
AST	1.055 (1.013–1.100)	0.011	1.001 (0.980–1.022)	0.962
ALT	1.031 (0.994–1.069)	0.103		
GGT	1.025 (1.006–1.045)	0.010	1.007 (0.993–1.021)	0.340

ALP – alkaline phosphatase, AST – aspartate aminotransferase, CCI – Charlson Comorbidity Index, GGT – gamma-glutamyl transferase, KP – Klebsiella pneumoniae

Parenteral nutrition is the administration of amino acids, glucose, lipids, electrolytes, vitamins, and trace elements to patients via a central or peripheral venous catheter. It is recommended for nutritional support if enteral feeding is contraindicated. Parenteral nutrition has been shown to increase the risk of CRKP, but the pathogenesis has not been fully elucidated [16]. In our study, parenteral nutrition was associated with a 3.7-fold higher risk of CRKP. It is unclear whether this increased risk of infection is related to the rich content or delivery method of parenteral nutrition [25]. Even if a patient does not have diabetes, they enter a diabetogenic state during parenteral nutrition because of the severity of their existing disease, the simultaneously administered dextrose-containing fluids, and their interaction [26, 27]. Glucose intolerance occurs with the aging process [28]. In the presence of acute metabolic stress, there is an increase in contraregulatory hormones such as catecholamine, glucagon, and corticosteroids, and hyperglycaemia occurs [28]. Insulin resistance is frequently detected in frail, older inpatients [29]. Although the patients' blood glucose levels were not analysed during parenteral nutrition support in our study, we suspect hyperglycaemia contributed to the risk of infection and acted as a growth medium for bacteria.

Although our study is the first to investigate the risk of CRKP infection in palliative care patients in our country, it has some limitations. The study was retrospective and observational, was conducted in a single centre, and included a limited number of patients.

CONCLUSIONS

The prevalence of CRKP is higher in patients receiving parenteral nutritional support. This demonstrates the importance of early transition to enteral nutrition if there is no contraindication. A high CCI value is a significant risk factor for the development of CRKP infection.

The authors declare no conflict of interest.

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